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From: Zeman, Mary
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Please send a copy of the following as soon as possible.
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Mary K. Zeman
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CM1 12A17
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TITLE: Application of artificial neural networks to the detection of Mycobacterium tuberculosis, its antibiotic resistance and prediction of pathogenicity amongst Mycobacterium spp. based on signature lipid biomarkers.
AUTHOR(S): Almeida, Jonas S. (1); Sonesson, Anders; Ringelberg, David B.; White, David C.
SOURCE: **Binary Computing in Microbiology, (1995) Vol. 7, No. 4-6, pp. 159-166.**

TITLE: Applying knowledge discovery to predict infectious disease epidemics.
AUTHOR: Raza Abidi, S.S.; Goh, A. (Sch. of Comput. Sci., Univ. Sains Malaysia, Penang, Malaysia)
SOURCE: PRICAI'98: Topics in Artificial Intelligence. 5th Pacific Rim International Conference on Artificial Intelligence. Proceedings
Editor(s): Lee, H.-Y.; Motoda, H.
Berlin, Germany: Springer-Verlag, 1998. p.170-81 of xix+646 pp. 18 refs.
Conference: Singapore, 22-27 Nov 1998
Sponsor(s): Center of the Int. Cooperation for Comput.; Microsoft; Sony Corp
ISBN: 3-540-65271-X

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TITLE: Applying knowledge discovery to predict infectious disease epidemics
AUTHOR: Abidi S S R (Reprint); Goh A
SOURCE: **LECTURE NOTES IN ARTIFICIAL INTELLIGENCE, (NOV-DEC 1998) Vol. 1531, pp. 170-181.**
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20.00

TITLE: Use of neural networks to define the genetic basis of HIV-1 resistance to d4T
AUTHOR: Larder, B.A.; Wang, D.
CORPORATE SOURCE: Virco UK Ltd, 184 Cambridge Science Park, Cambridge, UK
SOURCE: AIDS, (2000~~1000~~) vol. 14, pp. S12-S13.
Meeting Info.: 5th International Congress on Drug Therapy in HIV Infection. Glasgow (UK). 22-26 Oct 2000.
ISSN: 0269-9370.

TITLE (IN ENGLISH): Correlation of HIV protease structure with Indinavir resistance : a data mining and neural

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9 LATE BREAKERS

PL9.1

Activity of cyclosporin A in combination with highly active antiretroviral therapy in primary HIV-1 infection

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PL9.2

Prevention of nevirapine-associated exanthema using slow dose escalation, antihistaminics or corticosteroids

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The appearance of a rash is one of the most frequent and limiting side effects during the first 4 weeks of treatment with nevirapine (NVP). We explored the efficacy and safety of four different strategies for reducing the incidence of this complication.

Five-hundred and sixty-two patients were randomly assigned to accomplish the induction phase of NVP following either the standard (std) recommendation of 200 mg daily during the first 2 weeks (n=166), or any of four new strategies: i) adding loratadine 10 mg/12h during the first 2 weeks (n=93), ii) adding prednisone 50 mg each other day during the first 2 weeks (n=93), iii) using an slow escalating dosing, beginning with 100 mg daily the first week, and increasing the dose 100 mg weekly up to the full daily dose of 400 mg (n=107), and iv) combining both the addition of prednisone with the slow escalating dosing (n=103). A pharmacokinetic substudy was performed in 8 patients receiving 100 mg of NVP during the first week.

The incidence of rash and NVP discontinuation standard recommendation and the alternative approaches was:

Table PL9.2.

	STD	i	P	ii	P	iii	P	iv	P
n	166	93		93		107		103	
Exanthema	18.7%	8.8%	0.03	8.6%	0.02	11.2%	0.09	7.7%	0.01
Withdrawal	8.5%	5.3%	0.3	4.3%	0.2	4.7%	0.2	3.9%	0.1

P values compare the standard induction of NVP with the different new interventions. NVP plasma concentrations within the first week of treatment using 100 mg daily were above the IC90 for wild type HIV-1 in all instances.

In conclusion, the incidence of rash complicating the first few weeks of treatment with NVP can be diminished adding corticosteroids or antihistaminics for two weeks to the standard recommendation, or using a slow escalating dosing. This third approach is proven to be pharmacokinetically safe.

PL9.3

Severe liver toxicity in patients receiving two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor

I. Sanne on behalf of the FTC-302 Study Investigators and the FTC-302 Independent Clinical Steering Committee

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The use of some antiretroviral agents has been associated with hepatotoxicity. This toxicity has been associated with concomitant chronic viral hepatitis, alcohol use, hypersensitivity reactions and lactic acidosis.

FTC-302 is a randomized, placebo-controlled, double-blind study comparing emtricitabine (FTC) to lamivudine in a background of stavudine (d4T) and either nevirapine (NVP) (screening HIV-1 RNA ≤ 100 000 copies/ml) or efavirenz (EFV) (screening HIV-1 RNA > 100 000 copies/ml) in antiretroviral treatment-naïve HIV-infected patients in the Republic of South Africa.

A total of 468 patients were enrolled (385 in the NVP stratum, 83 in the EFV stratum). Fifty-nine percent of the patients are female; 87% of the patients are black. At the time of this report, all patients on treatment have completed 24 weeks. To date, treatment-emergent Grade 4 elevations in liver enzymes (ALT, AST, alkaline phosphatase, and total bilirubin) have been observed in 36 (9.4%) patients in the NVP stratum and in none of the patients receiving EFV. Of these 36 cases, 33 occurred within the first 4 weeks of therapy; the onset date for the remaining three cases was week 32. Of the 36 cases, one was HBsAg positive at screening with no evidence of active hepatitis, and two others had serological evidence of HCV infection. Incidence of grade 4 elevations was comparable between blinded treatment arms (9 versus 10%) and between blacks and non-blacks (9 versus 12%), but in females the incidence was twice that of males (12 versus 6%, $P = 0.05$). Two patients developed liver failure and died, one of whom was HBsAg positive at screening.

In this study, a high incidence of severe liver toxicity was observed, especially in women. Clinically these events were attributed to NVP in combination with d4T and blinded treatment medication. Consistent with recent recommendations, liver enzymes in patients receiving NVP with other antiretrowirals should be monitored closely, particularly during the first 8 weeks of use.

PL9.4

The C_{trough} inhibitory quotient predicts virologic response to ABT-378/ritonavir (ABT-378/R) therapy in treatment-experienced patients

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For protease inhibitors the C_{trough} inhibitory quotient (IQ:C_{trough}) is defined as the ratio of C_{trough} to the human serum-adjusted EC_{50}. Mean IQ: C_{trough} for current protease inhibitors (PIs) at labeled doses against wt HIV range from < 1 to 5, and the presence of fourfold or greater reduced baseline susceptibility (which effectively reduces IQ: C_{trough} to 1 or less) has been shown to be associated with diminished virologic response. Thus, IQ: C_{trough} may be used to estimate antiviral activity of protease inhibitors *in vivo*. ABT-378r is a new PI with a mean IQ for wt HIV of > 75. However, the IQ is reduced in many subjects previously treated with multiple PIs due to reduced baseline susceptibility. In a study of multiple PI-experienced NNRTI-naive patients treated with ABT-378/r+EFV+NRTIs, we assessed the relationship between virologic response and individual ABT-378 IQ:C_{trough} or C_{trough} values. The correlation between week 24 response (HIV RNA < 400 copies/ml) and IQ:C_{trough} or observed C_{trough} was analysed using Fisher's exact test. Across 56 subjects, the median IQ was 9.9 (range: 0.05–279) and median decrease in susceptibility to ABT-378 was 5.1 (range: 0.5–96). The observed response rate is highly correlated with IQ values, being 70%, 80%, and 100% for IQ of < 4, 4–15, and > 15, respectively ($P < 0.026$, n = 21, 15, and 16, respectively). In contrast, the observed response rate was not correlated with C_{trough}. The observed response rate is 86%, 74% and 85% for C_{trough} values of < 2.5, 2.5–4.5 and > 4.5 mcg/ml, respectively ($P < 0.741$, n = 14, 19 and 19, respectively). This analysis demonstrates that IQ:C_{trough}, which accounts for drug exposure as well as viral susceptibility, can be used to estimate antiviral activity in patients with reduced susceptibility. In contrast, PK parameters alone appear to be inadequate for assessing antiviral activity of PIs *in vivo*, particularly in previously treated patients.

PL9.5

Use of neural networks to define the genetic basis of HIV-1 resistance to d4T

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The complexity and diversity of HIV drug resistance mutation patterns makes it difficult to interpret genotypic testing results. This is especially in the case for d4T resistance, where associating specific mutations to phenotypic resistance remains a challenge. We present a systematic method to investigate the relationship between mutation patterns and corresponding phenotypic resistance using neural networks. In this study, three neural network models were developed to investigate how mutation patterns influence d4T resistance. One model was based on the 9 RT mutations listed in the Stanford sequence database associated with d4T resistance (62V, 69D, 69N, 69SXX, 75I, 75T, 116Y and 151M). The other were based on adding either 17 or 51 extra RT mutations present at relatively high frequency in d4T resistance

samples in our relational database. To train and test these neural network models, we used a total of 2286 samples, 188 of which were randomly selected as a test data set. An optimal solution for each of the models was obtained using the same training and testing data sets. The results demonstrated that the 9-mutation model gave a low resistance prediction rate (46%) using the independent test data set and in fact it was even difficult to obtain reasonable concordance in the training set (42%). However, the 26- and 60-mutation models could be well trained and also provided a higher prediction rate (65% and 68%, respectively) for resistance (defined as > 3-fold increase relative to a sensitive control) using the test data set. In order to discover which mutations had contributed to this improved prediction, discordant samples from the 9-mutation model were identified and the corresponding genotypes were analysed. In total, 15 additional mutations occurred in at least 30% of these samples, including 41L, 67N, 118I, 210W, 211K, 214F and 215Y. A number of these mutations had already been included in the 26- and 60-mutation models. In conclusion, these results show that at least 26 RT mutations may play a role in d4T resistance, including AZT resistance mutations. Refinement of these models should further enhance our understanding of the genetic basis of d4T phenotypic resistance.

PL9.6

Transmission and fitness of drug resistant strains of HIV

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The frequency with which transmission of drug resistant strains of HIV occurs is important for the future efficacy of treatment, and indirectly for the future course of HIV epidemics in the US and Europe. The aim of this study was to estimate the frequency of transmission of drug resistant strains of HIV relative to their prevalence in the HIV+ patient population.

The prevalence of resistance among newly infected individuals was estimated by phenotypic and genotypic assays; the proportion of potential transmitters of HIV carrying resistant strains was estimated in a retrospective clinic-based analysis.

Genotypic data from 111 individuals with primary HIV infection who had not received antiretroviral therapy revealed nine bearing mutations at primary resistance-associated amino acids in RT. The probable frequency of transmission of drug resistant strains in this group is therefore 9/111 = 8%. Defining 'potential transmitters' as individuals with plasma viral load (pVL) > 1500 copies/ml yields an estimate of 33% for the proportion of potential transmitters in the HIV+ population with resistant virus based on the known numbers failing therapy and assuming 50% of HIV+ individuals are attending a clinic. Comparing the proportion infected with the proportion of potential transmitters suggests that the fitness of drug-resistant strains at transmission is approximately 25% of wild-type. This is likely to be a minimum estimate as some resistant strains will have reverted to wild-type before sampling, but still suggests a substantial reduction in probability of transmission of resistant strains. Published estimates of fitness costs from plasma are lower than this (~1–10%), suggesting resistant viruses encounter additional barriers at transmission, perhaps relating to differential shedding into genital secretions or differential efficiency in establishing new infections.

10 ADVERSE EVENTS OF THERAPY

PL10.1

A perspective on the adverse events of HAART: an overview to include lipodystrophy

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PL10.2

Pathogenesis of lipodystrophy and metabolic disorders

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PL10.3

Lipodystrophy syndrome: developing a case definition

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There is no "gold standard" diagnostic test for lipodystrophy and no validated case definition. Several factors have hampered development of a definition of lipodystrophy: (1) it is unclear if lipodystrophy is one syndrome or more than one; (2) there are no objective diagnostic criteria for lipodystrophy; (3) possible features such as intra-abdominal accumulation, hyperlipidaemia and abnormal glucose tolerance are common in the general population; (4) there is high variability in normal body composition; and (5) at least two contributing factors (NRTIs and protease inhibitors) may lead to common physical and metabolic features.

Diagnostic criteria are needed for numerous reasons: to standardize recruitment of lipodystrophy studies, standardize reporting (particularly by industry to regulators), to compare drugs, drug combinations and drug classes, to compare different patient populations, to assist in identifying risk factors, and to assist clinicians in diagnosis

Under the auspices of the EMEA, an industry-sponsored study has begun in 37 sites worldwide that will endeavour to generate a valid, simple and broadly applicable case definition. The case-control approach developed by the American Rheumatology Association over the last 30 years for the diagnosis of a large number of rheumatic diseases has been adopted and will be discussed, along with the study outline.

PL10.4

Management of lipodystrophy and metabolic disorders

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Lipodystrophy (LD) and metabolic disorders are frequently encountered during antiretroviral chemotherapy (ART). The management of the complications (insulin resistance, diabetes mellitus and hyperlipidemia) include diet, exercise, drug therapy and modification of ART. Reduction of trunk fat can be achieved by physical exercise, anabolic steroids as well as recombinant human growth hormone (rhGH). With these measures an improvement of lean body mass and fat redistribution can be observed. In small studies the lipolyptic rhGH has been shown to increase body mass index, improve body composition, hip-waist ratio and serum lipid concentrations. Disadvantages include parenteral injections, costs prohibitive for many patients and (mostly transient) deterioration of insulin resistance with infrequent manifestations of frank diabetes mellitus. None of the few systematic studies so far could demonstrate a discernible increase of peripheral subcutaneous fat tissue strongly desired by most patients. Particularly the increase of LDL-, VLDL-, ApoB+E-cholesterol during ART indicate an increased risk of cardiovascular diseases, although time of observation on ART is not sufficiently long to reliably predict outcome. Therefore the indication for lipid lowering drugs is not clear or uniformly accepted. Only pilot studies with fibrates or statins have shown feasibility of reduction of lipids, but this additional medication as well as potential drug interactions particularly between protease inhibitors (PI) and statins have prevented widespread use and controlled studies. Frank diabetes can be treated with diet, sulfonurea drugs or insulin. To improve insulin sensitivity metformin or glitazones can be used. In a recent randomised controlled study with 500 mg metformin bid in 26 patients with HIV-LD hyperinsulinemia, weight and diastolic blood pressure were improved. Metformin was also associated with decrease in visceral and subcutaneous abdominal fat while lipoatrophy did not change during observation. A recent study with Troglitazone in the treatment non-HIV associated LD resulted in improved glucose and lipid control and increased body fat in patients with lipoatrophic diabetes. In a pilot study of 6 HIV-infected patients with ART associated diabetes better glucose control could be achieved, but a further increase of lipids (despite improved diabetes) was observed with no consistent pattern of change of body composition within six months of treatment. Con-